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MYRIAD GENETICS INC.
INTELLECUTAL PROPERTY DEPARTMENT
320 WAKARA WAY
SALT LAKE CITY, UT 84108

EXAMINER

WOLLENBERGER, LOUIS V

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| ART UNIT | PAPER NUMBER |
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1635

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/680,449

Applicant(s)

HUANG ET AL.

Examiner

Louis V. Wollenberger

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 November 2005 and 09 December 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 1-15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 16-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☒ Interview Summary (PTO-413)
Paper No(s)/Mail Date: 20060206
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Interview Summary

An Applicant-initiated interview was held on 12/8/05, following Applicants' first response, filed 11/9/05, to the previous Office Action mailed on 8/9/05. A summary of the interview is enclosed herewith. During the interview it was agreed that Applicants would file a supplemental reply, which was received by the Office as filed on 12/9/05. Thus, Applicants have filed two responses, dated 11/9/05 and 12/9/05, to the outstanding Office Action of 8/9/05.

Applicants' remarks filed on 11/9/05 and 12/9/05 are considered herein in view of the claims as amended on 12/9/05, which replace all prior versions of the claims, including those filed on 11/9/05.

Amendments/ Status of the Application

Claims 1–34 are pending. Claims 1-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicants' amendments to claims 16 and 18 and submission of new claims 21–34 are acknowledged. Also acknowledged are Applicants amendments to page 65 of the specification, filed on 11/9/05. As requested the amendments have been entered into the application.

Applicant's responses filed 11/9/05 and 12/9/05 have been considered. The following Final Office Action is offered in reply. Rejections and/or objections not reiterated from the previous Office Action mailed on Aug. 9, 2005, are hereby withdrawn. The following rejections

Art Unit: 1635

and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30 and 34 contain the trademark/trade name "FLAG". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a detectable peptide tag and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16–34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claims are drawn generally to kits comprising a plurality of expression vectors, cells, or organisms expressing chimeric RNA transcripts having different subject RNAs operably linked with the same “universal target RNA”; and a universal interfering RNA targeting said universal target RNA or an interfering RNA transcription vector that directs the expression of

said universal interfering RNA, wherein said universal interfering RNA is an siRNA or shRNA.

Claims 27–34 further limit the claims by stating that the chimeric RNA transcripts encode fusion proteins, having first and second amino acid sequences, wherein the second amino acid sequence is a detectable peptide tag.

Adequate written description does not exist in the instant application for all these kits. That is, the specification does not adequately allow persons of ordinary skill in the art to recognize that applicant(s) were in possession of the entire genus of universal interfering siRNAs, shRNAs, and expression vectors expressing said siRNAs and shRNAs targeting all possible universal target RNAs, including those that code for all possible detectable peptide tags such as those recited in claims 30 and 34, as now claimed in the instant claims. The instant application does not enable the skilled artisan to envision the structure of all possible siRNAs and shRNAs needed to target all possible universal target RNAs including all such target RNAs that code for detectable peptide tags.

MPEP §2163 states that “An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed (See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 [Fed. Cir. 2004])”

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry,

whatever is now claimed (pg. 1117). Because the level of skill and knowledge in the art increases over time, it is essential to determine possession as of the effective filing date.

In the instant case, the specification does not clearly allow persons of ordinary skill in the art to recognize that, as of the effective filing date, Applicants invented what is now claimed. The application does not enable the skilled artisan to clearly envision the detailed chemical structure of the encompassed genus of universal interfering siRNAs and shRNAs targeting the entire genus of universal target RNAs.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The instant application provides general guidance and two prophetic examples (pages 76–78) directed to the instantly claimed universal siRNAs and shRNAs. However, the disclosure is largely directed to the function of these siRNAs and shRNAs and does not convey with reasonable clarity the essential physical characteristics of the siRNAs and shRNAs themselves. In fact, the examples and the specification as a whole do little more than outline goals that might be achieved with the instantly claimed kits. Neither the instant application nor the prior art provide a well established correlation between the structure of the recited universal siRNAs, shRNAs and their function.

Describing an invention by its function alone is little more than a wish for possession; it does not satisfy the written description requirement.

MPEP §2163 states, in part: “[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).”

In the instant case, both the prior art and the instant application indicate a degree of unpredictability in the art as it relates to siRNA structure and function. For example, the instant application states at pages 4–5:

“Unfortunately, once a gene is selected for siRNA-induced silencing, the choice of which sequences to target by siRNAs is somewhat unclear. Towards this end, Holen and colleagues investigated the efficacy of siRNAs targeted to 30 different positions in the transcript of human coagulation trigger Tissue Factor (hTF) in a variety of human cell types in culture (See Holen et al., *Nucleic Acids Res.* 30:1757-1766 [2002]). (2002)). In this study several siRNAs corresponding to several target sequences located in hTF transcripts were synthesized and tested for their ability to induce silencing of the hTF gene. Of the several siRNAs synthesized and tested only a few resulted in a significant reduction in expression of hTF, suggesting that accessible siRNA target sites may be rare in some human mRNAs. Further, siRNAs targeting different sites in the hTF mRNA demonstrated striking differences in their ability to silence the expression of hTF. Although, strong positional effects were seen with the siRNAs tested, and regions of high GC content seem to be targeted less efficiently than those of low GC content, Holen and coworkers concluded that the factors determining the differences in siRNA efficiency remain unclear, and that susceptible RNAi target sites in some human genes may be rare. From a practical perspective, the results of Holen and colleagues suggest that it is difficult, if not impossible to predict, *a priori*, what sequences to target in a gene to target with siRNAs to induce efficient silencing by RNAi. In addition, there is a growing body of evidence that specific siRNAs selected to silence particular genes may produce unwanted and unanticipated off-target effects—altering the expression of untargeted RNA transcripts.” (underline added)

Thus, according to the specification and the prior art (Holen et al. [2002] *Nucleic Acids Res.* 30:1757-1766), it is difficult if not impossible to predict the structure of siRNAs that induce efficient gene silencing. The Examiner submits that this same limitation applies to the instantly

claimed “universal interfering RNAs.” A universal interfering siRNA, for example, required to target a particular universal target RNA, would be bound by the same rules and biochemical limitations of any other siRNA targeting any other mRNA transcript, whether the transcript is “chimeric” or not. Yet the instant application does not describe even a single exemplary interfering siRNA for any particular universal target RNA in any chimeric RNA transcript.

Additionally, the Examiner submits that it cannot be predicted *a priori* that any given universal interfering siRNA or shRNA will cause partial or complete degradation and inhibition of expression of the corresponding plurality of operably linked subject RNAs since the post-filing art teaches that

“...single siRNAs cause cleavage of the target mRNA at a single site, opening the possibility that the remaining 3'-fragment will be translated. The resulting N-terminal truncated protein may act as a dominant negative or constitutively active protein rather than as a true protein-null.” (Myers et al., US Patent Application Publication 2003/0224432, paragraph 6)

Thus, this teaching adds a further layer of unpredictability regarding the correlation between the structure and function of the claimed genus of universal interfering siRNAs. In view of the unpredictability in the art, the skilled artisan would need to look to the specification for guidance as to the structure of such siRNAs for targeting universal target RNAs operably linked to different subject RNAs; however no guidance is given.

The prior art clearly teaches methods for synthesizing candidate siRNAs; however the prior art and the instant application also recognize the need for empirical, trial and error testing to definitively establish siRNA function *in vitro* and *in vivo*. The instant application expressly states on page 7:

“Despite numerous studies in which siRNAs have been employed to induce gene silencing, no definitive rules have evolved to assist researchers in picking the most effective sequences to target within a given transcript. Although there are general guidelines to help researchers narrow

their choices for target sequences, researchers must still use a trial and error approach to empirically determine what individual siRNAs work best, and what siRNAs have minimal off-target effects.”

Without providing specific guidance as to the chemical/physical structure of even a single exemplary universal interfering siRNA, how, then, does the instant application enable the skilled artisan to envision the structure of all possible universal interfering siRNAs targeting every conceivable universal target RNA, as now claimed in claims 16 and 18, for example?

In sum, the prior art and the instant application indicates a fair degree of variability in the genus of universal interfering siRNAs and shRNAs.

In view of the breadth of the instant claims, it must be concluded that the instant application fails to describe the full scope of the instantly claimed inventions in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire genus of universal interfering siRNAs and shRNAs, as currently claimed, for targeting the entire genus of universal target RNAs.

Accordingly, the instant claims are rejected for failing to meet the written description requirement.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18–20 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Cox et al. (1998) *Genes & Development* 12:3715–3727.

Claim 18 is drawn to a kit comprising in a compartmentalized carrier: 1) a plurality of target cells or organisms each expressing a chimeric RNA transcript that has a subject RNA operably linked to a universal target RNA; and 2) a universal interfering RNA targeting said universal target RNA. Claim 19 limits Claim 18 by stating that the plurality of target cells or organisms are selected from the group consisting of plant cells, plant tissues, plant seeds, nematode cells, plants and nematodes. Claim 20 limits claim 18 by stating that the target cells or organisms are arranged in an addressable array on a solid support.

For purposes of examination of the instant claims, the ordinary meaning of the term “compartmentalized” has been applied since applicants do not specifically define the term in the specification. The Cambridge International Dictionary of English defines the term “compartmentalize” as a verb “to separate something into parts and not allow those parts to mix together.” The term “carrier” is taken to mean “a container for carrying,” (Merriam-Webster Online)—e.g., a bottle or a plastic tray.

Applicants define addressable arrays on pages 60, 61, 64, and 65, and state that such arrays may consist of at least 2 or more distinct addresses. The examiner submits that 2 separate vessels, bottles, containers, culture flasks, or test tubes containing different subject RNAs, or cells or organisms expressing different subject RNAs defines an addressable array and a compartmentalized carrier within the scope of Claim 20. Support for this interpretation is found on page 65 of the instant application, which states that “For macroarrays of transgenic organisms, arrays can be produced by arranging containers suitable for the culture of such organisms, in a regular configuration with defined addresses. Such arrays may consist of test tubes arranged in a rack, or culture vessels (e.g., flower pots) arranged on a tray, and such arrays may comprise 2, 3, 4, 6, 12, 18, 24, 48, 96, 120, 180, 240, 480, 960 or more transgenic organisms.”

Finally, it is noted that the instant application states (page 16) that: “The term ‘subject RNA,’ as used herein, refers to an RNA whose cellular concentration is to be altered, manipulated or reduced, or knocked down, by the action of an interfering RNA targeting the universal target RNA, but not the subject RNA.” The use of the term “refers to” indicates that a “subject RNA” is not to be narrowly limited to or defined as a particular species of RNA but is to be regarded, or classified within a general category or group. Thus, for purposes of this examination, the universal target and subject RNAs may be separate and distinct genes or simply different sequences or different yet contiguous regions within the same gene.

Similarly, the Examiner notes that neither the instant claims nor the specification specify strict demarcations between the beginning and end of the subject RNA sequence and the beginning and end of the target RNA, and there is no requirement either in the claims or in the

Art Unit: 1635

instant specification that the subject RNA be strictly 5', centered, or 3' of the target RNA. Figure 1 of the instant application shows all three of these embodiments. Similarly, there is no restriction on the number of regions in any chimeric RNA transcript that might serve as possible universal targets, nor any restriction or clear definition as to which regions or sequences within a given chimeric RNA transcript are to be considered as the subject RNA and which regions are to be considered as the universal target RNA. In fact, many combinations are possible and many embodiments that may be considered to fall within the scope of the instant invention, including those chimeric RNA transcripts and organisms expressing such transcripts taught by Cox et al.

Cox et al. teach a plurality of *C. elegans* (nematode) organisms expressing at least two chimeric RNA transcripts within the scope of the instant invention. In particular, Cox et al. teach that *C. elegans* express at least two genes, *prg-1* and *prg-2*, which are nearly identical in structure, having regions of homology and non-homology (page 3718). In fact, the two genes are said to be 90% identical to each other over their full length and 98% identical at the carboxyl terminus (page 3718). The two genes are said to differ primarily in that *prg-1* is 60 amino acids longer at the amino terminus than *prg-2* (3718). Accordingly, the Examiner submits that each gene encodes a "chimeric transcript" comprising a "universal target RNA," the sequences that are shared, and a "subject RNA," the sequences that differ, within the scope of the instant invention as now claimed.

Cox et al. state that "Given the extremely high homology between *prg-1* and *prg-2*, we used an anti-*prg-1* RNA for injection to interfere with the function of both genes (see Materials and Methods. Herein, we designate the F₁ progeny of the injected worms as *prg-RNAi* worms for simplicity." (page 3721)

Accordingly, Cox et al. teach a “universal interfering RNA,” a dsRNA (see page 3725) targeting “chimeric RNA transcripts” that comprise the same target RNA and different subject RNAs within the scope of the instant invention, and a plurality of organisms, nematodes, expressing said transcripts. Furthermore, each transcript may be considered to code for a fusion protein, having first and second amino acid sequences, within the scope of instant claim 31.

Response to Applicants' Arguments

Applicants' arguments presented on 11/9/05 and 12/9/05 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

Art Unit: 1635

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval system (PAIR). Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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Art Unit: 1635

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Louis V. Wollenberger, Ph.D.
Examiner
Art Unit 1635
February 7, 2006



SEAN MCGARRY
PRIMARY EXAMINER
1635